Basics of Genetic Assessment and Counseling

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What is Genetic Counseling?

- **communication process**
- address individual concerns relating to development / transmission of hereditary disorder
- **consultand** = individual who seeks genetic counseling
- strong communicative and supportive element so that those who seek information are able to reach their own fully informed decisions without undue pressure or stress

What Information should be provided?

- medical diagnosis and its implications in terms of prognosis and possible treatment
- mode of inheritance of disorder and the risk of developing and/or transmitting it
- choices or options available for dealing with the risks

Steps in Genetic Counseling

- **Diagnosis** - based on history, examination and investigations
- Risk assessment
- **Communication**
- Discussion of Options
- **Long-term contact** and support

Establishing the Diagnosis

- **most crucial step** in any genetic counseling
- if incorrect - totally misleading information could be given with tragic consequences
- reaching diagnosis involves three fundamental steps
  - taking a history
  - examination
  - undertaking appropriate investigations

Establishing the Diagnosis

- Information about consultand's family is obtained by skilled genetics nurse or counselor
- pre-clinic telephone or home visit is helpful
- clinic visit - full examination
- appropriate tests - chromosomes, molecular studies, referral to specialists (neurology, ophthalmology)
- **PROBLEM - Genetic Heterogeneity, and etiologic heterogeneity**

Genetic Heterogeneity

- def - disorder that can be caused by more than one genetic mechanism

- **Ehlers Danlos** **AD, AR, XR**
- **Charcot-Marie-Tooth** **AD, AR, XR**
- **Retinitis Pigmentosa** **AD, AR, XR**

Genetic Heterogeneity

- **Charcot-Marie-Tooth** - also known as hereditary motor and sensory neuropathy type I **(HMSN I)** has been shown to result from a small duplication on short arm of chromosome 17

- If found - this would aid in counseling

Etiologic heterogeneity

- even though firm diagnosis - several **causes** may be possible
- eg. Deafness and non-specific mental retardation
  - environmental or genetic factors
  - empirical risks can be used although these are less satisfactory than risks based on specific diagnosis

Calculating and Presenting the Risk

- **straightforward counseling situations** - little more than knowledge about Mendelian inheritance is needed
- Problems:
  - delayed age of onset
  - reduced penetrance
  - use of linked markers can make calculations more complex

Presenting the Risk

- does not simply involve conveying stark risk figures in isolation
- parents must be given as much **background** as possible
- as rule of thumb: **recurrence risks should be quantified, qualified and placed in context**

Quantification

- Most prospective parents will have some concept of risks
- Experience demonstrates that some **common misinterpretations occur**
  - a risk of 1 in 4 may be remembered as 4 to 1, 1 in 40, or even 14% !!!
  - the risk only applies to every fourth child !!

Quantification

- vital to emphasize that the risk applies to **each child,** and that **chance does not have a memory**
- genetic counselors should not be seen exclusively as prophets of doom
  - for example a family with a risk of 1 in 25 for NTD, should be reminded that in 24 of 25 cases the child will be normal

Qualification - Nature of a Risk

- factor which influences parents when deciding whether to have another child is **nature** of the **long-term burden** associated with a risk rather than precise numerical value
- “high-risk” of 1 in 2 for a **trivial problem** (polydactaly) will not deter many families while a “low risk” of 1 in 25 for a disabling condition (NTD) can have a significant deterrent effect

Discussing the Options

- provide consultands with **all** information needed to arrive at **their own** informed decision
- details of all the choices open to them - include a complete discussion of **reproductive options**
- alternative approaches to conception - AID, donor ova
- review of **techniques, limitations and risks** associated with methods available for prenatal diagnosis

Communication and Support

- Communication - two way process
- Counselor provides information
- Receptive to fears and aspirations: expressed or unexpressed by consultant
- Information - present in clear, sympathetic and appropriate manner

Communication and Support

- Individual or couple will be **extremely upset** when first made aware of a genetic disorder
- complex psychological and emotional factors can influence counseling dialogue
- setting - **agreeable, private and quiet, with ample time for discussion and questions**

Counseling

- Session can be so **intense and intimidating** that amount and accuracy of information retained is very disappointing
- **Letter** summarizing the topics discussed at counseling session is often sent to family
- **Follow-up home visit or clinic appointment** to clarify any confusing issues

Directive or Non-Directive

- Universal agreement - non-coercive with **no attempt to direct** consultand along a course of action
- Non-judgmental - even if decision reached seems ill-advised
- Unwise to answer “What would you do if placed in my position?” rather consideration should be given to **consequences of each possible course of action**
- **remember - counsultand has to live with consequences!!!**

Special Problems in Genetic Counseling

- Consanguinity and Incest
- Adoption and genetic disorders
- Disputed Paternity

Consanguinity and Incest

- Consanguineous Marriage is between blood relatives who have at least one common ancestor no more remote than great-great grand parent
- Incest - union between first degree relatives (brother-sister, parent-child)

Proportion of Genes Shared

Genetics relationship of partners	Proportion shared genes	Risk of abnormality in offspring
First Degree parent-child brother-sister	1/2	50%
Second Degree uncle-niece aunt-nephew	1/4	5-10%
double first cousins	1/8	3-5%

Frequencies of three main types of abnormalities in the children of incestuous relationships

- Mental Retardation 25%
- Autosomal recessive disorder 10-15%
- Congenital malformations 10%

Marriage Between Blood Relatives

- Increased risk of AR disorders in future offspring
- Probability that first cousins will have a child with AR disorder is 3%

Paternity Testing

- genetic fingerprinting using minisatellite repeat sequence probes
- pattern of DNA fragments generated by those probes is ***so highly polymorphic that the restriction map is unique to each individual***
- specific as fingerprints

Chromosome Disorders Introduction

- 1956 - technique for chromosome analysis became reliable
- to date, more than 100 chromosome syndromes have been reported
- 47, XX/XY, +21
- Klinfelters (47XXY)
- Turners (45,X)

Incidence: Chromosome Abnormalities

- 15 - 20% of all recognized pregnancies end in spontaneous miscarriages
- 50% of all SAB have a chromosome abnormality
- incidence of chromosome abnormaility at conception is 20%
- by birth - 0.5 - 1%

Chromosome Abnormalities in SAB

Abnormality	Incidence (% of total)
Trisomy 13	2
16	15
18	3
21	5
other	25
Monsomy X	**20**
Tripoloidy	15
Tetraploidy	5
Other	10

Incidence: Chromosome Abnormality at term

Abnormality		Incidence per 10,000 births
Autosomal trisomy	13	2
	18	3
	21	15
Sex Chromosomes		
Female births	45, X	1
	47,XXX	10
Male births	47, XXY	10
	42, XYY	10

Chromosome Deletion Syndromes

- Microscopically visible deletions of terminal portions of:

  Chromosome 4p - Wolf Hirshorn
  Chromosome 5p - Cri-du-Chat
  severe mental retardation
  failure to thrive
  Both very rare - 1/50,00 births

Microdeletion Syndromes

- **high resolution** prometaphase banding and **FISH**
- Some microdeletions involve **loss of only a few genes** at closely adjacent loci **“Contiguous gene syndromes”**
- In others - several loci are involved

Microdeletion Syndromes

Syndrome	Chromosome
Williams	7
Langer-Giedion	8
WAGR	11
Angelman	15
Prader-Willi	15
Rubenstien Taybi	15
Miller-Dieker	17
Smith-Magennis	17
DiGeorge	22
Shprintzen	22

Lessons form Microdeletion Syndromes

- Retinoblastoma
- Wilms’ tumor
- Angelman and Prader-Willi S.
- DiGeorge and Shprintzen S.

Retinoblastoma

- 5% of children with RB had other abnormalities - ie Mental Retardation
- in several children a constitutional interstitial deletion of 13 q 14
- this deletion at 13 q 14 is the locus for the AD form of RB

Wilm’s tumor

- Wilm’s tumor (hydronephroma)
- Aniridia (absent Iris)
- Genital abnormalities
- Retardation of growth and development
- WAGR syndrome

WAGR Syndrome

- interstitial deletion of particular region on short arm of chromosome 11

- gene location - WT1

Wilms Tumor

- Family cases of AD Wilms' tumor have been shown not to be linked to this locus (WT1)
- rare overgrowth syndrome - Beckwith-Wiedemann S. is associated with a deletion and imprinting of a separate locus on 11p.

Angelman and Prader-Willi S.

Angelman - inappropriate laughter, convulsions, poor coordination (ataxia) and mental retardation

Prader-Willi - extremely floppy (hypotonic) in early infancy, marked obesity, and mild to moderate mental retardation later in life.

Imprinting - Angelman + PWS

- If deletion occurs de novo on paternally inherited number 15 chromosome
  - PWS - 15q (15q 11-12)
- If deletion occurs de novo on maternally inherited number 15 chromosome
  - AS - 15q (15q 11-12)

AS and PWS

- non deletion cases also exist and are often due to uniparental disomy (UPD)
  - AS - both #15 chromosomes being paternal in origin
  - PWS - both #15 chromosomes being maternal in origin

AS and PWS

- loss at a critical region from paternal #15 chromosome causes PWS
- loss of identical critical region from maternally inherited #15 chromosome causes AS

Triploidy
69, XXX; 69, XXY; 69, XYY

- relatively common in SAB
- **rare in live-born infants**
- IUGR: in utero-relative preservation of head size with small trunk
- syndactaly of 3rd and 4th fingers and/or 2nd and 3rd toes
- dispermy or fertilization by diploid sperm

Hypomelanosis of Ito

- **Mosaicism** for diploidy/triploidy identified
- skin: alternating patterns of normally pigmented and depigmented streaks which correspond to embryological developemental lines of skin known as Blashko's lines
- most are **moderately retarded** and have **convulsions** which are difficult to treat.